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USSR PROGRESS IN THE FIELDS OF HEMATOLOGY AND BLOOD TRANSFUSION

[Numbers in parentheses refer to appended sources.]

Twenty-five years ago, the first institute of blood transfusion in the world was organized in Moscow. At present, this institute is called the Central Order of Lenin Institute of Hematology and Blood Transfusion (TsOLIPK, Department of Clinical Medicine, Academy of Medical Sciences USSR).

Being continually concerned with questions of public health and military-medical defense, the institute expanded its activities and became the central organization directing all aspects of blood transfusion and hematology in the USSR. In the process of this expansion, a network of republican, kray, oblast, and municipal affiliates (blood transfusion stations) was opened throughout the country by the institute. The municipal stations have the task of organizing blood-transfusion units at city district hospitals (rayonnyye stantsii). Among the affiliates of the Central Order of Lenin Institute, there are prominent scientific institutions like the Leningrad, Tbilisi, Kharkov, and Minsk institutes, to which special hematological clinics are attached.

The fundamental problem of blood transfusion, that of preserving blood, was successfully solved the USSR scientists. Originally, in 1930, the blood could be preserved in a completely fresh (physiologically unchanged) state for only 2 weeks. This period has been extended to 30-40 days and is being extended still further at present. Considerable work has been done on the development of effective preservation media and antiseptics to be used in preservation. Both the Central Order of Lenin Institute and the peripheral stations participated in work which attempted to establish whether preserved blood is therapeutically equivalent to fresh blood. This question has been decided in the affirmative. One of the most recent achievements is development of the dextrose-saccharose-citrate solution TsOLIPK No 8, which permits preservation of erythrocytic mass for 30 days without hemolysis. The erythrocytic mass can be thus transported to other cities.

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In this connection, one may also mention the special ampules TsIPK (Central Institute for Blood Transfusion) No 1 and TsOLIPK No 2.

The antitoxic and antibacterial properties of blood are well known from clinical experience. This applies particularly to transfusions of immune blood for the treatment of infectious diseases. Work in this field has been done by N. N. Burdenko, V. V. Akkerman, S. P. Zayeva, K. M. Dvolaytskaya-Barysheva, and B. N. Rubinshteyn. As far as the stimulating effect of blood transfusion is concerned, A. A. Bogomolets's hypothesis of colloidoclastic shock is no longer adequate.

In the field of hemotherapy, extensive work on the effect of blood transfusions after heavy blood losses and shock has been carried out by the Central Order of Lenin Institute. The results of this work were of particular benefit during World War II. No less important is the problem of hemotherapeutic treatment of suppurative and septic processes. The therapeutic effect of blood transfusions, particularly transfusion of blood of another group, in this class of diseases was already recognized 20 years ago by S. I. Spasokukotskiy, et al. The Central Order of Lenin Institute is working on the differentiation of indications for this type of treatment. The impression prevails at the institute that hemotherapy of suppurative and septic conditions is the best method of treatment, particularly in combination with the application of antibiotics.

The work of A. N. Kryukov, Kh. Kh. Vlados, F. P. Vinograd-Finkel', I. I. Yurovskaya, and Ye. V. Shamshina in the field of erythrocytotherapy has opened up new ways for the treatment of leukoses as well as other diseases. The combination of transfusions of erythrocytic mass with penicillin therapy, which has been proposed by them is being applied extensively in the treatment of acute leukoses, hypoplastic anemias, and adverse agranulocytary reactions.

Particularly noteworthy is the beneficial effect of serum transfusions, especially of concentrated solutions of dry serum, in the treatment of protein insufficiency. The best results in nutritive dystrophy were obtained when massive quantities of serum were injected daily or within short intervals (1-2 days).

Extensive work on blood transfusions, carried out after operations for cancer, indicates a beneficial effect, although there are no definite indications that metastases are prevented. In the field of hemotherapy of infectious diseases, work on the transfusion of immune blood was expanded considerably during recent years. This method was found particularly effective in acute and chronic dysentery. Investigations on the transfusion of blood and its components for the treatment of liver and kidney diseases have yielded promising results as far as kidney diseases are concerned. Work carried out at the Central Order of Lenin Institute and its affiliates on the Rh factor clarified the significance of this factor in posttransfusion complications and the etiology of congenital hemolytic disease.

The USSR blood-transfusion service was able to supply a sufficient quantity of preserved blood and blood substitutes during World War II. The work on blood substitutes was stimulated by the war. In this connection, development of salt solutions used alone or in combination with blood or serum may be mentioned. Practical experience has shown that human plasma or serum are the best blood substitutes and that the use of whole blood often may be dispensed with entirely. One of the most significant achievements in connection with the use of these natural blood substitutes was solution of the problem of drying plasma and serum. Work on the subject was done at the Central and Leningrad Institutes of Blood Transfusion. The convenience of transportation and practically unlimited storage qualities of dry serum resulted in the very successful application of this preparation during World War II. An important phase of activity was concerned with the fractionation of human plasma in order

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to obtain therapeutic agents. In the course of this work, new and original methods for the preparation of gamma-globulin, albumin, fibrin films, and thrombin were proposed. These products are now being tested clinically on an extensive scale.

Of considerable significance is the work of Soviet scientists on the production of preparations from heterogenous blood. At the Leningrad Institute of Blood Transfusion, A. N. Filatov developed methods producing fibrin preparations from the blood of cattle. L. G. Bogomolova proposed a new preparation, a hemostatic sponge which produces a good therapeutic effect and which is prepared from human and animal plasma. During World War II, the problem of preparing substitutes for human serum in the form of colloidal protein solutions was solved by the Central Order of Lenin Institute. This refers to N. A. Fedorov's, P. S. Vasil'yev's, and M. A. Lisitsin's "colloidal infusin," N. G. Belen'kiy's and D. A. Arapov's species nonspecific serum, and V. A. Belits'er's heterogenous serum. B. I. Zbarskiy, et al., proposed a new method of preparing a hydrolyzate of animal proteins for the treatment of hypoproteinemia. D. L. Rubinshteyn, D. M. Grozdov, and R. A. Rutberg developed a new sonic method for lasting preservation of plasma with retention of fibrin.

In the field of hematology, important results were also achieved by Soviet workers. After the completion of extensive experimental and clinical observations, a unitary theory of blood formation was drawn up. Work in this connection was done by A. A. Zavarzin, A. D. Timofeyevskiy, A. N. Kryukov, M. I. Arinkin, Kh. Kh. Vlados, and G. K. Khrushchov. At the Central Order of Lenin Institute, original ideas concerning the etiology, pathogenesis, and therapy of the most important diseases of the blood-forming system (pernicious anemia, chlorosis, erythremia, Werlhof's disease, and leukoses) were developed. Valuable contributions were made by G. F. Lang and his collaborators, who initiated the physiological school of hematology. By developing a practical method for the study of the bone marrow during life, M. I. Arinkin, Stalin Prize Laureate, opened up wide perspectives for solving complicated problems connected with normal and pathological conditions in the blood-forming system. I. A. Kassar'skiy, A. F. Korovnikov, and M. Abramov developed methods of puncturing the spleen and lymphatic nodes for diagnostic purposes.

Of fundamental importance were data proving that leukoses are closely related to malignant tumors from the pathogenic standpoint, as could be shown by producing experimental leukosis in animals with the aid of endogenic and exogenic cancerogens (A. A. Bogomolov and M. O. Kaushenbakh). An ingenious method of determining homopoietic substances in various liquids of the organism was developed. This replaced Singer's method, which was completely unspecific. Clinicoexperimental investigations of the role played by the stomach and the liver in hemopoiesis were carried out by Kh. Kh. Vlados, N. A. Fyedorov, M. S. Dul'tsin, P. M. Al'perin, and A. A. Bagdasarov. The introduction of tissue-culture methods into hematology represented a considerable advance. In this connection, the work of A. D. Timofeyevskiy, P. I. Benevolenskiy, and G. K. Khrushchov on the biology of cells and their capacity to undergo tissue differentiation in vitro may be mentioned.

Of theoretical importance was the study of the restorative, adaptive, and regulatory role of the nervous system in hemopoiesis, carried out in recent years (Dzhavadyan). When the peritoneal or upper cervical ganglia of dogs are removed or damaged, or the vagus is cut, the animals develop anemia. The anemia, which is a result of corticovisceral disturbances, is spontaneously checked for a while. According to Asratyan, this phenomenon indicates mobilization by the organism of compensatory mechanism under the regulatory action of the central nervous system. According to Raushenbakh, excessive straining of the nervous system of mice by M. K. Petrova's method expedites the appearance of spontaneous or induced leukosis.

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The Central Order of Lenin Institute of Hematology and Blood Transfusion is studying problems related to hemolysis (endogenic hemolytic substances have been isolated by Rubinshteyn and Ginzburg), the biology of erythrocytes (S. Ye. Severin), and the mechanism of enzymatic systems participating in the oxydative processes which take place in tissues and organs in anemias and leukoses (Derviz and Bulanova). Metabolism of blood pigments (of hemoglobin, prophyryns, and iron) was investigated in cases of anemia and during the period of blood regeneration by donors (Belousov). Shifts in protein fractions by the electrophoretic method (G. Ya. Rozenberg and Astrakhan), as well as the structural viscosity of blood (P. S.?, Vasil'yev Kozlova) under dynamic conditions in leukoses and cancer, were investigated. In this manner, extensive data were accumulated for use in establishing general relationships in the field of hematology.

According to results obtained in the Cytological Laboratory (Terent'yeva), lymphocytes of normal blood develop polypotentiality under condition of tissue culture in the sense that they have a capacity toward differentiation in various directions. The investigator established in this work that the capacity towards differentiation in leukosis patients varies depending on the severity of the course of the disease.

The achievements of the Hematological Clinic of the Central Order of Lenin Institute deserve particular attention. In regard to pernicious anemia, workers at that clinic published the first known description of coma perniciosum and defined more precisely the pathogenesis of this disease. They also developed methods of treatment, among which blood transfusion is the most effective. Chronic hypoplastic perniciosiform anemia was differentiated (Kh. Kh. Vlados). This disease was later described by foreign authors under the name of achrestic anemia. Methods of treating relapses of pernicious anemia and of so-called macrocytic anemias were developed (Shamshina). Konchalovskiy and M. S. Dul'tsin differentiated advanced chlorosis and described the clinical aspects of this disease.

An original and effective method of treating hemolytic anemias with plasma, followed by transfusion of erythrocytic mass, was proposed (Kh. Kh. Vlados, A. P. Belousov, and Osechenskaya). The effectiveness of erythrocytotherapy in combination with administration of antibiotics in anemic conditions was established. This method of treatment is also effective in hypoplastic anemias and agranulocytosis.

Hemorrhagic diatheses, particularly Werlhof's complex of symptoms, were studied in combination with surgicoclinical aspects (S. I. Spasokukotskiy, N. A. Bakulev, and I. I.? Kazanskiy). Indications for splenectomy in this disease are determined on the basis of a clinicohematological differentiation of the condition, while the role of the vascular factor in its genesis was confirmed by clinical and experimental observations. A special form of hemorrhagic diathesis was differentiated in schizophrenia (Kh. Kh. Vlados and Gol'denberg), a finding which is of great theoretical as well as practical importance.

M. I. Arinkin's school of hematology, in the persons of V. A. Beyer and Geyro, is continuing to develop in its work the concept of the nervous regulation of hemopoiesis. One may mention in this connection Beyer's observations on the modification of hemopoiesis in wounded persons, as well as his original hypothesis to the effect that the functional condition of the brain marrow forms a reflection of the reactive state of the organism and, therefore, may serve as an indication of the qualitative peculiarities of this state. Arinkin's method of investigating the bone marrow of living subjects has already been mentioned. The results of investigations of this type, on correlation with data on peripheral blood, led to new relationships which aid in the clinical evaluation of the hematogram. Arinkin's work stimulated application of cytological methods of diagnosis in clinical practice. I. Kassirskiy's and

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G. Alexeyev's work is concentrated on the investigation by Arinkin's method of the dynamics of blood formation in the bone marrow when various pathological conditions are present. Shmelev, Kassirskiy, and Abramov developed methods of cytological diagnosis by the punctation of lymphatic nodes, the spleen, the liver, and other organs.

Of interest is the work of Makarevich, Krayevskiy, and Lazovskiy, who established that the fundal part of the stomach is of importance in developing the internal factor in cases of pernicious anemia. This finding was confirmed by the experimental and pathologic-anatomic data of Fox and Castle. Experimental investigations carried out on dogs by Kh. Kh. Vlados, A. A. Bagdasarov, M. S. Dul'tsin, and N. A. Fyedorov showed that on removal of one of the parts of the stomach (the fundal or pyloric), the remaining part contributes to compensation and elimination of the temporary anemia resulting from the experiment. Lazovskiy demonstrated that the histological structure of the mucous membrane of the stomach's remaining part is modified in the course of this compensatory adaptation. The group of investigators headed by Vlados has also studied the role of the liver in hemopoiesis [see above].

One of the most important achievements of USSR hematology is the work by L. F. Larionov, Stalin Prize Laureate [according to Spravochnik Akademii Meditsinskikh Nauk SSSR, Moscow, 1946, Larionov is director of the Laboratory of Experimental Cancer Therapy, Institute of Oncology, Academy of Medical Sciences USSR] on the application of a new chemotherapeutic method of treating leukemia and lymphogranulomatosis with embikhin, a substance of the nitrogen mustard class. (2) The compound embikhin was synthesized by Prof. V. G. Nemets of the Leningrad Technological Institute imeni Lensovet. Larionov's investigations were started in 1947 before publications by foreign authors on the therapeutic application of compounds of this class appeared in print, so that the method developed and applied in the USSR is entirely different. Its distinguishing characteristics, as compared with the US method of applying a brief shock treatment with standardized maximum doses and repeating this treatment on recurrence, are mild and gradual treatment, individualized dosage, and prevention of recurrences by the treatment. By histological examination of samples taken from the bone marrow, spleen and lymph organs of experimental animals (rabbits), it could be established that embikhin exerts its strongest inhibiting effect on granulocytopenia, followed by that on lymphopoiesis, and, finally the weakest effect, on erythropoiesis.

While experimental results obtained by L. L. Malyugina indicate that embikhin probably will not find extensive application in the treatment of carcinomas, its effect on the metabolism of nucleoproteids and some clinical results obtained with it (especially on metastases of breast cancer into lymphatic nodes) give rise to the hope that this drug will be of help in the therapy of malignant tumors other than lymphogranulomatosis (for instance, treatment in combination with X-ray therapy of metastases which cannot be operated on, etc.).

A thorough toxicological investigation of embikhin was carried out, using rats and rabbits as experimental animals. The qualitative results roughly corresponded to those obtained by Graef et al., American Journal of Pathology, Vol XXIV, No 1, 1948. The "therapeutic" dose of embikhin for rats (i.e., a dose which affects the blood-forming system only) was found to be 0.2 mg/kg of body weight and amounted to one tenth of the lethal dose. (3)

The 25th anniversary of the Central Order of Lenin Institute of Hematology and Blood Transfusion was commemorated by the 29th Expanded Plenary Session of the Scientific Council of the institute, which was held at Moscow in May 1951. In his introductory speech, Prof. A. A. Bagdasarov, director of the institute, presented some of the information outlined in the general progress report given above [cf. 1]. Prof. N. A. Bakulev, in a paper entitled "Some Problems of Surgery in the Light of I. P. Pavlov's Teaching," recommended hemotherapy in

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combination with narcotics for the treatment of shock. Prof V. I. Kazanskiy according to Spravochnik Akademii Meditsinskikh Nauk SSSR, Moscow 1946, Kazanskiy is head, Division of Surgery, and Member of Scientific Council, TsOLIPK<sup>7</sup> and V. A. Agranenko reported on an original method of chemical neurotomy, anesthesia of the chest cavity behind the chest wall, to be used as a measure for preventing shock in extensive thoracic operations. In connection with their report, these investigators raised the question of expanding the blocking of reflexogenic zones in combination with blood transfusion and application of drugs as a method of treating shock.

A report presented by A. A. Bagdasarov dealt with the application of hemotherapy in hypoproteinemic conditions. In this report, a basis was laid from the pathogenetic standpoint for the use of whole blood or its components in various conditions. Electrophoretic investigations showed that in septic conditions there is a sharp lowering of the albumin content in the plasma of the patient's blood, while the globulin content rises. Under the circumstances, a favorable effect is obtained by infusing an albumin solution.

Of great interest was the pioneering proposal to use the whole blood or blood preparations as a means of tissue therapy in a number of diseases (Prof Ye. N. Klyukvina, and Prof. Filatov). The beneficial effect of transfusions of preserved blood in cases of bronchial asthma and ulcers was noted in that connection. The method was found to be of advantage in the treatment of inflammatory infiltrates, as well as of trophic and varicose ulcers (G. S. Ivakhnenko, L. I. Mikhaylova, V. F. Bogdanskii, et al.).

Mention is to be made of a new method of applying serum in septic forms of scarlet fever. In cases of hemolytic anemia, the effectiveness of therapy with plasma, followed by transfusion of whole blood, as well as clinical use of the iron salt of ascorbic acid, may be noted (Prof Kh. Kh. Vlados and A. F. Belousov).

Prof F. R. Vinograd-Finkel' presented a report on problems of blood preservation. In the course of this report, he made efforts to prove USSR priority in work in this field.

Prof S. Ye. Severin summarized the characteristics of the metabolism of erythrocytes, calling attention to progress in the study of carbohydrate-phosphorus metabolism, in particular. He emphasized the significant role of glucose as a nutritive substrate for erythrocytes and that of glycolysis, stating that both favor the preservation of erythrocytes. Prof P. S. Vasil'yev, on the basis of work on blood proteins, brought out the important function which glucose and saccharose play in stabilizing the protein structures of erythrocytes during blood preservation. He emphasized the role of the fission of lipid-protein complexes in the process of hemolysis and in blood conservation.

It was further mentioned in the discussion which took place during the meeting that the theory of blood conservation based on biochemical and physico-colloidal investigations carried out at the institute permits a rational approach to the search for preservatives that are capable of prolonging the period during which blood can be stored to 40-50 days. In the course of this work new substances for preserving blood were proposed: polyalcohols (F. G. Ginzburg), the stabilizer synanthrol (V. D. Yankovskiy, A. G. Polyboyarinova), the antiseptically acting antibiotic synthomycin (G. A. Krotova and M. Ye. Depp) and a prescription, on the basis of which alcohol and other drugs which aid in bringing about therapeutic blocking can be added to preserved blood, was developed (Prof I. I. Fyedorov). It was brought out during the discussion that further work on prolonging the time during which blood can be stored should develop in two directions: (1) preservation of metabolic processes and of the structure of erythrocytes during the whole period of storage; and (2) reversible suppression of the level of metabolism of erythrocytes so that a state of anabiosis is established.

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A paper by D. M. Grozdov outlined achievements in the field of blood substitutes and blood preparations. This author explained the advantages of USSR methods of producing blood substitutes and antishock liquids, the preparation of which is based on I. P. Pavlov's physiological teaching (the liquids of Prof E. A. Asratyan, Prof N. A. Fyedorov, D. M. Grozdov, and others). He mentioned in particular work on methods for the production of dry plasma and dry serum which has been carried out at the institute, stating that ten different preparations are at present being produced from human blood and several from animal blood.

In a report dealing with the production of blood preparations from human plasma, G. Ya. Rosenberg told about the work done by USSR scientists in that field. He stated that the Central Order of Lenin Institute of Hematology and Blood Transfusion, in cooperation with the Moscow Institute imeni I. I. Mechnikov, has carried out an investigation on methods for the fractionation of blood proteins. As a result of this work, in which Prof A. A. Bagdasarov, G. Ya. Rosenberg, and L. S. Pozhariyskaya participated, five therapeutic preparations (gamma-globulin, albumin, fibrin films, thrombin, and erythrocytic mass) are being produced simultaneously in the course of the same process. The majority of these preparations have been tested clinically and are being introduced into medical practice. As a result of this work, the whole approach to the treatment and utilization of blood destined for the production of anti-measles serum has been modified. The use of this serum has been abandoned; a concentrated gamma-globulin preparation which contains measles antibodies is being used instead.

On the basis of material presented at the meeting and statements made during discussions which took place there, a lot of ground remains to be covered in research on the production and preservation of plasma preparations. Thus, the question of prolonged conservation of the protein composition of blood plasma has not yet been completely solved. Furthermore, the question of enrichment of plasma with biological and pharmacologically active substances such as hemoglobin, vitamins, narcotic agents, etc., requires additional thorough investigation. Also, further research on the application of preparations from heterogenous blood is necessary.

The plenary session passed a resolution to the effect that the most important and pressing task is study of the mechanism of the regulation of hemopoiesis, this being the basis of the whole field of both theoretical and practical hematology. In this study, the effect of the nervous system under both normal and abnormal conditions must be emphasized. Another task, according to the resolution, is clinical investigation of the effect of chemotherapeutic agents in combination with new methods of treatment of hematological disturbances such as sleep therapy, the novocain block according to A. V. Vishnevskiy and A. D. Speranskiy, and application of cytotoxic serum prepared according to the principles laid down by I. I. Mechnikov and A. A. Bogomolets.

In the concluding phase of the meeting, Kh. Kh. Vlados summarized the present state of hematology in a report entitled "Results and Perspectives of the Development of USSR Hematology" [cf. 2].

In view of its scope, this meeting must be regarded as an all-Union conference on questions of hematology and blood transfusion.(4)

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3. "Treatment of Leukemia and Lymphogranulomatosis With Embikhin" (Lecheniye Belokroviya i Limfogrannlomatoza Embikhinom), L. F. Larionov, Press of the Academy of Sciences USSR, Moscow, February 1951, 99 pp
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